Experimental Parasitology 134 (2013) 368–373

Contents lists available at SciVerse ScienceDirect

Experimental Parasitology

journal homepage: www.elsevier.com/locate/yexpr

Renal parenchyma developmental plasticity in mice infected with *Schistosoma mansoni*, whose mothers were malnourished during lactation

Christiane Leal Corrêa [a,b,1], Júlio Cesar Antônio Moreira [b,1], Augusto César Miranda Vilela [b,1], Elaine de Oliveira [c,1], Egberto G. Moura [c,1], Patrícia Cristina Lisboa [c,1], José Roberto Machado-Silva [a,*,1]

[a] *Laboratory of Helminthology Romero Lascasas Porto, Department of Microbiology, Immunology and Parasitology, Faculty of Medical Sciences, Immunology and Parasitology, School of Medical Sciences, Biomedical Center, Rua Prof. Manoel de Abreu 444/5° Floor, Vila Isabel, 20511-070 Rio de Janeiro, RJ, Brazil*
[b] *Laboratory of Experimental Pathology, Gama Filho University, Rua Manoel Vitorino, 553 – Piedade Rio de Janeiro, 20740-900 Rio de Janeiro, RJ, Brazil*
[c] *Laboratory of Endocrine Physiology, Roberto Alcantara Gomes Biology Institute, State University of Rio de Janeiro, Rua Prof. Manoel de Abreu 444/5° Floor, Vila Isabel, 20511-070 Rio de Janeiro, RJ, Brazil*

HIGHLIGHTS

- Malnutrition during periods in development may have long-term effects in the adult.
- We examine parasitological behavior and histopathological.
- For the first time, this study describes the changes of the renal parenchyma.
- Induced by postnatal malnutrition associated with infection caused by *Schistosoma mansoni*.

GRAPHICAL ABSTRACT

Biometrical parameters of the kidney and its parenchyma in schistosomiasis-infected adult male mice whose mothers were fed with normal (C), caloric- restricted (CR) or protein-restricted (PR) diet during lactation.

	GROUPS					
	Uninfected			Infected		
	CONTROL	CR	PR	CONTROL	CR	PR
Kidney weight (g)	0.41 ± 0.00	0.39 ± 0.01	0.40 ± 0.06	0.37 ± 0.04	0.49 ± 0.01 ^{a,b}	0.43 ± 0.01 ^{c}
Perimeter (μ)	220.01 ±7.86	220.14±11.07	213.86±7.06	247.64±8.41	278.24±15.16^{a}	258.83±13.89^{a}
Space of Bowman (μ)	9.11±0.71	8.56±1.61	11.99±0.70	10.85±1.30	13.33±1.40^{a}	4.66±1.34^{a}
Area of the glomerulus (μ)	3312.90±316.17	3133.41±303.80	2967.38±200.06	4438.40±305.64^{a}	6105.74±744.39^{a}	4437.26±505.63^{a}
Number of glomerulus	132±8	94±14^{b}	78±10^{b}	118±5	80±8^{b}	62±10^{b,c}

a infected vs uninfected; *b* vs C; *c* vs CR or PR. Data presented as means ± standard error of the mean (significant difference: $p < 0.05$).

ARTICLE INFO

Article history:
Received 21 June 2012
Received in revised form 18 March 2013
Accepted 20 March 2013
Available online 6 April 2013

Keywords:
Developmental plasticity
Lactation
Mice
Schistosoma mansoni
Renal parenchyma
Glomerulus
Bowman space

ABSTRACT

Effects of maternal malnutrition during lactation on the kidneys in mice infected with *Schistosoma mansoni*. Kidneys from programmed infected mice and their respective controls fed a normal diet (23% protein), a protein-restricted group (PR) (8% protein) and a caloric-restricted group (CR) (according to the PR group intake) evaluated by biometry, morphometry and histopathology. Both PR and CR groups showed a reduction in the number of glomeruli when compared with the control group (CR: −29% vs C; PR: −41% vs C; $p < 0.05$) as well as infected mice (ICR: −32% vs IC; IPR: −47% vs IC; $p < 0.05$). Among infected mice, ICR group showed higher kidney weights (+18% vs IC and +12% vs IPR; $p < 0.01$). The ICR and IPR groups showed largest perimeter and area when compared to the corresponding uninfected group (ICR vs CR: +26%; IPR vs PR: +21%, $p < 0.05$) and area (ICR vs CR: +95%; IPR vs PR: +50%, $p < 0.05$). The ICR group showed an increase of within Bowman (CR vs ICR: +56%, $p < 0.05$), whereas Bowman's space was reduced (PR vs IPR, −61%; $p < 0.05$). Conclude that malnutrition during lactation programmed the metabolic state of the host, resulting in the evolution of the histology of the renal parenchyma.

1. Introduction

Neglected tropical diseases (Hotez et al., 2008), nutritional disorder like undernourishment (Casapía et al., 2007; Gyorkos et al., 2011) and chronic kidney disease (Nugent et al., 2011) represent public health concerns because affect vulnerable communities in developing countries. Epidemiological data have shown detrimental effects of malnutrition and parasitic infection on health, cognition and behavior in preschool-aged children affected with concurrent morbidities (Muniz et al., 2002; Hughes and Kelly, 2006; Casapía et al., 2007; Jardim-Botelho et al., 2008).

Schistosomiasis mansoni, caused by the blood dwelling fluke *Schistosoma mansoni*, is one the most prevalent neglected tropical water-borne disease (Gryseels et al., 2006). It is estimated that

* Corresponding author.
E-mail address: machado@uerj.br (J.R. Machado-Silva).
[1] Brazilian Council of Science and Technology (CNPq) fellow.

0014-4894
http://dx.doi.org/10.1016/j.exppara.2013.03.025

among 120 million symptomatic individuals, 20 million often develop severe morbidity (Chitsulo et al., 2000; Steinmann et al., 2006), which is characterized by hepatic fibrosis, portal hypertension, ascites, esophageal varices, collateral circulation and splenomegaly (van der Werf et al., 2003; Gryseels et al., 2006; Lambertucci, 2010). Epidemiological studies have shown that schistosomiasis is related to changes in the renal parenchyma, mediated by immune complexes and even today, schistosomiasis-related renal injury remains a major problem in Brazil (Rodrigues et al., 2010).

Metabolic programming is defined as a biological phenomenon that determines the relationship between physical and chemical stimuli in critical periods of early life, such as gestation and/or lactation, with the future functional status (de Moura et al., 2008). This concept has been questioned mainly because it gives an idea of a deterministic phenomenon instead of a process that can be modulating during development by several factors. So, the term "developmental plasticity" is now used because it better reflect this biological phenomenon (Gluckman and Hanson, 2007). In fact, animal studies have reported that maternal malnutrition during the critical period of lactation may have deleterious effects in the adult life of the offspring, even if the animal had free access to normal diet after weaning (Passos et al., 2000, 2004; Vicente et al., 2004; Moura et al., 2007; Fagundes et al., 2007, 2009; Lisboa et al., 2008). Previously, we reported that that neonatal malnutrition during lactation affects the outcome of schistosomiasis in mice (Corrêa et al., 2011).

Although schistosomal glomerular disease in hepatosplenic schistosomiasis (Andrade and Van Marck, 1984), protein-energy malnutrition in the chronic renal failure (Abraham et al., 2003) and an association between maternal low-protein and kidney dysfunction in adult life have been reported (Mesquita et al. 2010), little is known regards the effects of neonatal malnutrition on the offspring kidney in the acute schistosomiasis in mice. Thus, the present study was addressed to evaluate the association between the long-term effect of malnutrition during lactation and the infection caused by *S. mansoni* upon the kidney and its parenchyma.

2. Materials and methods

2.1. Ethics statement

The use of the animals according to our experimental design was approved by the Animal Care and Use Committee of the Biology Institute of the State University of Rio de Janeiro (CEUA/232/2008), which based its analysis on the principles adopted and promulgated by Brazilian Law 11.794/2008 (Marques et al., 2009).

Table 1
Composition of the experimental diets for rodents.

	Control diet[a] (g/kg)	Low-protein diet[b] (g/kg)
Ingredients		
Soybean+wheat	230.0	80.0
Cornstarch	676.0	826.0
Soybean oil	50.0	50.0
Vitamin mix[c]	4.0	4.0
Mineral mix[c]	40.0	40.0
Macronutrient composition (%)		
Total energy (kJ/kg)	17,038.7	17,038.7
Protein	23.0	8.0
Carbohydrate	66.0	81.0
Fat	11.0	11.0

[a] Standard diet for rodents (Nuvilab, NUVITAL Nutrientes, Paraná, Brazil).
[b] The low-protein diet was prepared in our laboratory using the control diet and replacing part of its protein with cornstarch. The amount of the latter ingredient was calculated to make up for the decrease in energy content due to protein reduction.
[c] Vitamin and mineral mixtures were formulated to meet the AIN-93G recommendation for rodent diet and contain the recommended amount of iodine.

2.2. Animal model

Details of the *S. mansoni*-mouse model employed in the current investigation have been described elsewhere (Corrêa et al., 2011). Briefly, mouse dams obtained from Oswaldo Cruz Foundation animal facility were separated in control diet (C) with 23% protein, protein-restricted diet (PR) with 8% protein and caloric-restricted diet (CR) (fed according to the PR group intake) (Table 1). Neonatal malnutrition began at the time of the pup's birth (day 0) and ended at weaning (21 days). After weaning, offspring received a normal diet. At the age of 60 days, the offspring were infected with 50 *S. mansoni* cercariae (BH strain, Brazil) by transcutaneous route, and infection allowed to mature for nine weeks representing the acute phase of infection. Mouse pups were divided into six groups: uninfected control (C), uninfected protein-restricted diet (PR), uninfected caloric-restricted diet (CR), infected fed control diet (IC), infected fed protein-restricted diet (IPR) and infected fed caloric-restricted diet (ICR).

2.3. Histopathology

Kidneys from programmed mice and their controls were excised and weighed. Kidneys samples were fixed in 10% buffered

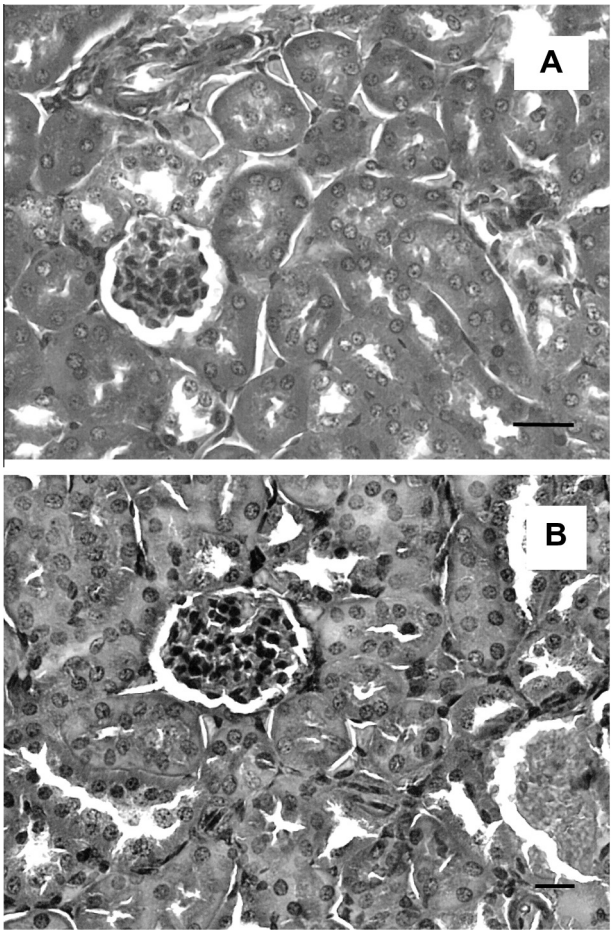

Fig. 1. Histopathological analysis of kidney sections from adult control and infected control offspring. (A) Stained sections from adult control showing glomeruli and convoluted tubules with preserved parenchyma (Masson's trichrome stain) (Bar = 20 mm); (B) stained sections from adult infected control showing glomeruli with a small increase and convoluted tubules with preserved parenchyma H&E (Bar = 20 mm).

formalin and processed for routine histopathological analysis. Five-micrometer sections were stained with haematoxylin and eosin, Masson's trichrome or Picrosirius.

2.4. Morphometric analysis

Representative images were captured with a light microscope (Olympus BX50 Tokyo, Japan). Morphometric measurements of area, perimeter and Space of Bowman were made on digitally captured images (Nikon Eclipse E200 camera Nikon DS-Fi1), using Image Pro Plus software (Media Cybernetics, Silver Spring, MD, USA).

3. Statistical analysis

Results are expressed as mean values ± standard error of the mean. The GraphPad Prism 4 (GraphPad Software, Inc, La Jolla, CA, USA) was used for statistical analyses and graphics. Results were analysed by one-way analysis of variance and Newman–Keuls multiple comparison tests. Other experimental data (infected vs. uninfected group) were analyzed by Student's unpaired t test and differences were considered significant at $p < 0.05$.

4. Results

4.1. Renal histopathology and morphometry

The weights of kidneys from uninfected mice children were not statistically different and showed preserved renal parenchyma (Figs. 1–3A).

There was no leukocyte infiltrate present in the renal parenchyma in groups of infected animals. ICR offspring displayed higher kidney mass (+30%, $p < 0.0001$). The PR and CR offspring presented lower number of glomeruli (CR: −29% vs C; PR: −41% vs C, $p < 0.05$), independent of the infected status (ICR: −32% vs IC; IPR: −47% vs IC, $p < 0.05$), as depicted in Table 2.

As shown in Table 2, the glomeruli perimeter was higher in ICR and IPR groups (ICR vs CR: +26%; IPR vs PR: +21%, $p < 0.05$) as well as the area of glomeruli was higher in all infected group (IC vs C: +34%; ICR vs CR: +95%; IPR vs PR: +50%, $p < 0.05$). ICR offspring show glomerular hypertrophy and increased urinary space of Bowman's (+56% vs CR; $p < 0.05$) (Fig. 2B), while this parameter was lower in IPR offspring (−61% vs PR, $p < 0.05$) (Fig. 3B). The infection did not cause changes in Bowman's space in the control group (Fig. 1A and B).

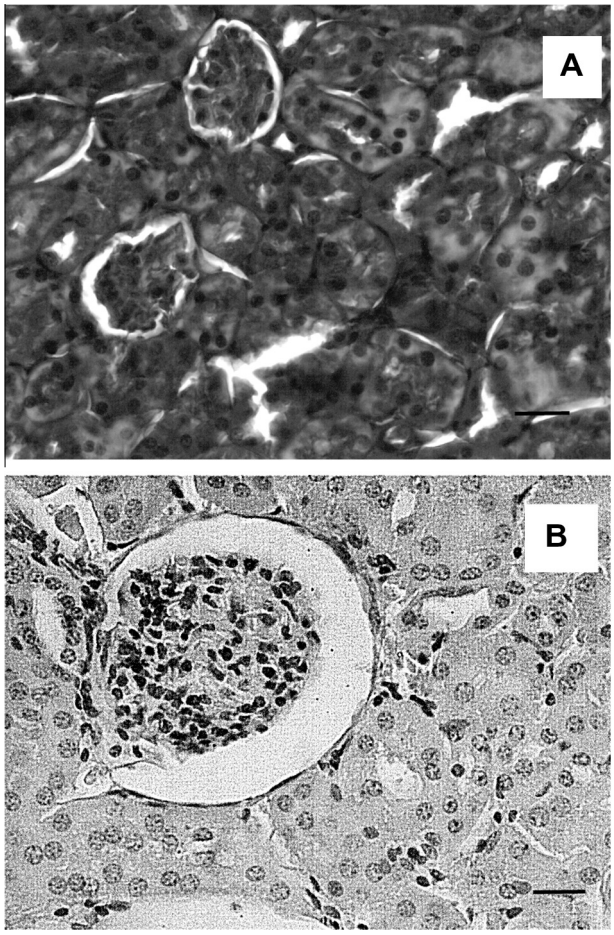

Fig. 2. Histopathological analysis of kidney sections from adult caloric-restricted and infected caloric-restricted off spring. (A) Stained sections from adult kidney parenchyma from adult caloric-restricted showing glomeruli and convoluted tubules with preserved parenchyma (Masson's trichrome stain) (Bar = 20 mm); (B) stained sections from adult infected caloric-restricted showing glomerular hypertrophy and increased urinary space of Bowman H&E (Bar = 20 mm).

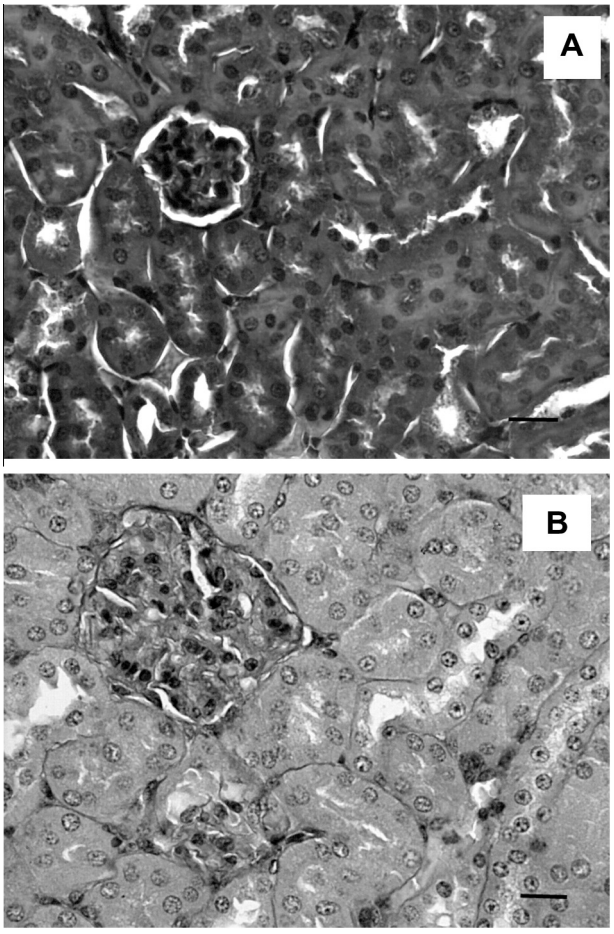

Fig. 3. Photomicrographs of kidney sections from adult protein-restricted and infected protein-restricted offspring. (A) Stained sections from adult protein-restrited showing glomeruli and convoluted tubules with preserved parenchyma (Masson's trichrome stain) (Bar = 20 μm); (B) stained sections from adult Infected protein-restricted showing glomerulus with reduced space urinary Bowman (H&E) (Bar = 20 μm).

Table 2
Biometrical parameters of the kidney and its parenchyma in schistosomiasis-infected adult male mice whose mothers were fed with normal (C), caloric-restricted (CR) or protein-restricted (PR) diet during lactation.

Groups						
Uninfected				Infected		
	Control	CR	PR	Control	CR	PR
Kidney weight (g)	0.41 ± 0.00	0.39 ± 0.01	0.40 ± 0.06	0.37 ± 0.04	0.49 ± 0.01[a],[b]	0.43 ± 0.01[c]
Perimeter (μ)	220.01 ± 7.86	220.14 ± 11.07	213.86 ± 7.06	247.64 ± 8.41	278.24 ± 15.16[a]	258.83 ± 13.89[a]
Space of Bowman (μ)	9.11 ± 0.71	8.56 ± 1.61	11.99 ± 0.70	10.85 ± 1.30	13.33 ± 1.40[a]	4.66 ± 1.34[a]
Area of the glomerulus (μ)	3312.90 ± 316.17	3133.41 ± 303.80	2967.38 ± 200.06	4438.40 ± 305.64[a]	6105.74 ± 744.39[a]	4437.26 ± 505.63[a]
Number of glomerulus	132 ± 8	94 ± 14[b]	78 ± 10[b]	118 ± 5	80 ± 8[b]	62 ± 10[b],[c]

Data presented as means ± standard error of the mean (significant difference: $p < 0.05$).
[a] infected vs uninfected.
[b] vs C.
[c] vs CR or PR.

5. Discussion

Glomerulonephritis, a major cause of chronic kidney disease worldwide, presents with various histological and clinical manifestations that are related to its severity and duration resulting in diverse clinical outcomes. Immune-mediated injury of the resident glomerular cells plays a critical role in many forms of glomerular injury and mounting evidence indicates that both humoral and cell-mediated mechanisms are involved. The goal of our present study was evidence that glomerular diseases caused by schistosomiasis may be more intense when associated with malnutrition during lactation.

The phenomenon of metabolic programming has received considerable interest over the last decade. Lactation is a critical period during the development of mammals and is important in the establishment of programming (Moura et al., 2008). Rat studies have demonstrated that dietary restrictions lead to changes in body weight and disruption of various physiological processes (Passos et al., 2000, 2004; Vicente et al., 2004; Fagundes et al., 2007, 2009; Moura et al., 2007; Lisboa et al., 2008). For instance, metabolic programming by undernutrition throughout lactation (Luzardo et al., 2011) or during pregnancy (Mesquita et al. 2010) leads to renal changes. Our prior studies demonstrated that neonatal malnutrition of offspring during lactation resulted in alterations of body mass probably due to hypophagia (PR mice) and hyperphagia (CR mice). Also, the outcome of acute schistosomiasis was affected with liver damage (Corrêa et al., 2011).

The acute schistosomiasis is characterized by a strong host immune response against parasite larvae and both gut-associated worm and soluble egg antigens (Houba, 1979; Andrade, 2009). With ageing of the infection, the immune response to parasite antigens is down-regulated (Boros, 1989; Sadler et al., 2003). In regards to disease progression, the hepatosplenic form is characterized by an extensive hepatic fibrosis, portal hypertension, ascites, esophageal varices, collateral circulation and splenomegaly (van der Werf et al., 2003; Gryseels et al., 2006; Lambertucci, 2010). In addition, renal pathology has been associated with the hepatosplenic phase in both human (Andrade and Van Marck, 1984; Ramos and Andrade, 1987; Abensur et al., 1992; Rodrigues et al., 2010) and animal studies (Sobh et al., 1996).

In this study, we observed renal involvement in the acute phase that not only contrast to above studies but also highlights pathologic features of other organ than liver (Corrêa et al., 2011). As kidney weight, perimeter, space of Bowman and glomerulus area were not altered in uninfected CR and PR offspring when adult, it is possible that the normal diet offered after weaning was effective to prevent these kidney changes. However, it was not efficient to prevent the reduction of glomeruli number, which was previously reported in rats (Langley-Evans et al., 1999; Woods et al., 2001; Ots et al., 2004; Zandi-Nejad et al., 2006). The loss of glomeruli can be associated with systemic hypertension and proteinuria in individuals with low birth weight and in the experimental models of caloric or protein restriction (Langley-Evans et al., 1999; Woods et al., 2001; Ots et al., 2004; Pires et al., 2006; Zandi-Nejad et al., 2006). Also, in our laboratory in a model of early weaning we evidenced important renal dysfunction in the adult progeny, also characterized by glomerulosclerosis and peritubular fibrosis (Passos et al., 2011).

Investigations concerning the pathogenesis of glomerular lesions found that liver damage has a role (Digeon et al., 1979). Previously, we showed that ICR offspring had liver and spleen enlargement and higher (78%) exudative-productive granuloma, high concentration of collagen and areas of fibrosis caused by retention of eggs, resulting in intrahepatic hypertension (Corrêa et al., 2011). Therefore, it was not surprising that kidney weight was also higher than other offspring.

Human studies demonstrated that membranoproliferative glomerulonephritis is one of the most common renal lesion in chronic schistosomiasis (van Velthuysen, 2000). Additionally, this type of glomerulonephritis correlates with the degree of associated schistosomal hepatic fibrosis (Barsoum, 2003; Santos et al., 2011).

Even today, schistosomiasis related renal injury remains an important problem in Brazil (Rodrigues et al., 2010). Studies have shown that schistosomiasis is related to changes in the renal parenchyma, mediated by immune complexes (Andrade and Van Marck, 1984), autoimmune component and portal shunting (Van Velthuysen, 2000). In fact, some studies demonstrated an association between Th2 cytokine production and intensity of infection (Zwingerber et al., 1991; Williams et al., 1994; Araújo et al., 1994; Viana et al., 1994; Fallon et al., 2000; Abdulla et al. 2011). In the kidney, the Th2-mediated response is characterized by formation of immune complexes and deposition in the glomerulus, which is usually followed by complement activation (Nussenzveig et al., 2002). On the other hand, the Th1-mediated response is characterized by infiltration of circulating mononuclear cells and crescent formation. Both responses are capable of releasing mediators that are responsible for functional and structural changes as seen in primary glomerular diseases. Importantly, these apparently discrepant mechanisms of immune reactions, the Th1 and Th2 responses, are not always mutually exclusive and operate in a coordinated manner in glomerular injury, depending on etiology and pathological stages. Immune complexes are either formed in the systemic circulation and localize in the glomerulus through passive trapping or are formed *in situ* and form immune deposits locally. An antibody either binds specific antigens intrinsic to the glomerulus, or soluble antigens that

become localized due to charge interactions with the glomerular capillary wall or by nonspecific uptake by the mesangium. Importantly, human studies have demonstrated that schistosomal glomerulopathy is also observed in patients with hepato-intestinal schistosomiasis, in which porto-systemic shunts are not evidenced (Nussenzveig et al., 2002). Our experimental model closely resembles those human studies.

The programming during lactation led to a decreased number of glomeruli in the infected offspring, in which IPR groups showed lowest number. In fact, it was reported that protein energy malnutrition in maternal sheep has potential nephrogenic impairment during pregnancy (Lloyd et al., 2012).

We found higher perimeter glomeruli and area in ICR and IPR groups when compared to CR and PR in the adult malnourished mice. This finding has been observed in previous studies (Coutinho, 2004), demonstrating a significant inflammatory response given the presence of *S. mansoni* eggs in their hosts (Sleigh et al., 1986).

The ICR group showed higher of Bowman's space, and the IPR group showed lower of Bowman's space. Lloyd et al. (2012) showed that protein restriction causes changes in kidney parenchyma with reduced number of glomeruli. It is related to overweight that leads to compensatory mechanism with glomerular hypertrophy and increased Bowman's space.

6. Concluding remarks

The findings of the present study extend and reinforce the theory of neonatal programming, suggesting that both protein and energy restriction during lactation have a prominent effect on the course of acute *S. mansoni* infection and renal parenchyma in adult offspring mice. The maternal malnutrition causes long-term effects in the kidney of the host, with lower number of glomerulous, while *S. mansoni* infection affects more the glomeruli area, independent of maternal nutritional status.

Conflicts of interest

The authors have no conflicts of interest concerning the work reported in this paper.

Acknowledgments

We gratefully acknowledge financial support from the National Council for Scientific and Technological Development – PIBIC/CNPq.

References

Abdulla, M.H., Lim, K.C., McKerrow, J.H., Caffrey, C.R., 2011. Proteomic identification of IPSE/alpha-1 as a major hepatotoxin secreted by *Schistosoma mansoni* eggs. PLoS Negl. Trop. Dis. 5 (10), 1365–1368.

Abensur, H., Nussenzveig, I., Saldanha, L.B., Pestalozzi, M.S., Barros, M.T., Marcondes, M., Barros, R.T., 1992. Nephrotic syndrome associated with hepatointestinal schistosomiasis. Rev. Inst. Med. Trop. Sao Paulo 34, 273–276.

Abraham, G., Varsha, P., Mathew, M., Sairam, V.K., Gupta, A., 2003. Malnutrition and nutritional therapy of chronic kidney disease in developing countries: the Asian perspective. Adv. Renal Replace. Ther. 10, 213–221.

Andrade, Z.A., Van Marck, E., 1984. Schistosomal glomerular disease. (A review). Mem. Inst Oswaldo Cruz 79, 499–506.

Andrade, Z.A., 2009. Schistosomiasis and liver fibrosis. Parasite Immunol. 11, 656–663.

Araújo, M.I., Bacellar, O., Ribeiro-de-Jesus, A., Carvalho, E.M., 1994. The absence of gamma-interferon production to *S. mansoni* antigens in patients with schistosomiasis. Braz. J. Med. Biol. Res. 27, 1619–1625.

Barsoum, R.S., 2003. Schistosomiasis and the kidney. Semin. Nephrol. 23 (1), 34–41.

Boros, D.L., 1989. Immunopathology of *Schistosoma mansoni* infection. Clin. Microbiol. Rev. 2, 250–269.

Casapía, M., Joseph, S.A., Núñez, C., Rahme, E., Gyorkos, T.W., 2007. Parasite and maternal risk factors for malnutrition in preschool-age children in Belen, Peru using the new WHO Child Growth Standards. Br. J. Nutr. 98, 1259–1266.

Chitsulo, L., Engels, D., Montresor, A., Savioli, L., 2000. The global status of schistosomiasis and its control. Acta Trop. 77, 41–51.

Corrêa, C.L., Lisboa, P., Oliveira, E., Moura, E.G., Oliveira, R.M.F., Gomes, C.A., Machado- Silva, J.R., 2011. The outcome of acute schistosomiasis infection in adult mice with postnatal exposure to maternal malnutrition. Mem. Inst. Oswaldo Cruz 106, 584–593.

Coutinho, E.M., 2004. Malnutrition and hepatic fibrosis in murine schistosomiasis. Mem. Inst. Oswaldo Cruz 99, 85–92.

De Moura, E.G., Lisboa, P.C., Passos, M.C., 2008. Neonatal programming of neuroimmunomodulation role of adipocytokines and neuropeptides. Neuroimmunomodulation 15, 176–188.

Digeon, M., Droz, D., Noel, L.H., Riza, J., Rieumailhol, C., Bach, J.F., Santoro, F., Capron, A., 1979. The role of circulating immune complexes in the glomerular disease of experimental hepatosplenic schistosomiasis. Clin. Exp. Immunol. 35, 329–337.

Fagundes, A.T.S., Moura, E.G., Passos, M.C.F., Santos-Silva, A.P., Oliveira, E., Trevenzoli, I.H., Casimiro-Lopes, G., Nogueira-Neto, J.F., Lisboa, P.C., 2009. Temporal evaluation of body composition, glucose homeostasis and lipid profile of male rats programmed by maternal protein restriction during lactation. Horm. Metab. Res. 41, 866–873.

Fagundes, A.T., Moura, E.G., Passos, M.C., Oliveira, E., Toste, F.P., Bonomo, I.T., Trevenzoli, I.H., Garcia, R.M., Lisboa, P.C., 2007. Maternal low-protein diet during lactation programmers' body composition and glucose homeostasis in the adult rat offspring. Br. J. Nutr. 98, 922–928.

Fallon, P.G., Richardson, E.J., McKenzie, G.J., McKenzie, A.N.J., 2000. Schistosome infection of transgenic mice defines distinct and contrasting pathogenic roles for IL-4 and IL-13: IL-13 is a profibrotic agent. J. Immunol. 164, 2585–2591.

Gluckman, P.D., Hanson, M.A., 2007. Developmental plasticity and human disease: research directions. J. Intern. Med. 261, 461–471.

Gryseels, B., Polman, K., Clerinx, J., Kestens, L., 2006. Human schistosomiasis. Lancet 368, 1106–1118.

Gyorkos, T.W., Maheu-Giroux, M., Casapía, M., Joseph, S.A., Creed-Kanashiro, H., 2011. Stunting and helminth infection in early preschool-age children in a resource-poor community in the Amazon lowlands of Peru. Trans. R. Soc. Trop. Med. Hyg. 105, 204–208.

Hotez, P.J., Bottazzi, M.E., Franco-Paredes, C., Ault, S.K., Periago, M.R., 2008. The neglected tropical diseases of Latin America and the Caribbean: a review of disease burden and distribution and a roadmap for control and elimination. PLoS Negl. Trop. Dis. 2, e300.

Houba, V., 1979. Experimental renal disease due to schistosomiasis. Kidney Int. 16, 30–43.

Hughes, S., Kelly, P., 2006. Interactions of malnutrition and immune impairment, with specific reference to immunity against parasites. Parasite Immunol. 28, 577–588.

Jardim-Botelho, A., Brooker, S., Geiger, S.M., Fleming, F., Souza Lopes, A.C., Diemert, D.J., Corrêa-Oliveira, R., Bethony, J.M., 2008. Age patterns in undernutrition and helminth infection in a rural area of Brazil: associations with ascariasis and hookworm. Trop. Med. Int. Health 13, 458–467.

Lambertucci, J.R., 2010. Acute schistosomiasis mansoni: revisited and reconsidered. Mem. Inst. Oswaldo Cruz 105, 422–435.

Langley-Evans, S.C., Welham, S.J.M., e Jackson, A.A., 1999. Fetal exposure to a maternal low protein diet impairs nephrogenesis and promotes hypertension in the rat. Life Sci. 64, 956–974.

Lisboa, P.C., Fagundes, A.T., Denolato, A.T., Oliveira, E., Bonomo, I.T., Alves, S.B., Curty, F.H., Passos, M.C., Moura, E.G., 2008. Neonatal low-protein diet changes deiodinase activities and pituitary TSH response to TRH in adult rats. Exp. Biol. Med. 233, 57–63.

Lloyd, L.J., Foster, T., Rhodes, P., Rhind, S.M., Gardner, D.S., 2012. Protein energy malnutrition during early gestation in sheep blunts fetal renal vascular and nephron development and compromises adult renal function. J. Physiol. 590, 377–393.

Luzardo, R., Silva, P.A., Einicker-Lamas, M., Ortiz-Costa, S., Tavares do Carmo, M.G., Vieira-Filho, L., Paixão, A.D.O., Lara, L.S., Vieira, A., 2011. Metabolic programming during lactation stimulates renal Na^+ transport in the adult offspring due to an early impact on local angiotensin II pathways. PLoS One 6, e21232.

Marques, R.G., Morales, M.M., Petroianu, A., 2009. Brazilian law for scientific use of animals. Acta Cir. Bras. 24, 69–74.

Mesquita, F.F., Gontijo, J.A.R., Boer, P.A., 2010. Maternal undernutrition and the offspring kidney: from fetal to adult life. Braz. J. Med. Biol. Res. 43, 1010–1018.

Moura, E.G., Santos, R.S., Lisboa, P.C., Alves, S.B., Bonomo, I.T., Fagundes, A.T., Oliveira, E., Passos, M.C., 2008. Thyroid function and body weight programming by neonatal hyperthyroidism in rats – the role of leptin and deiodinase activities. Horm. Metab. Res. 40, 1–7.

Moura, E.G., Lisboa, P.C., Custódio, C.M., Nunes, M.T., Souza, K.P., Passos, M.C.F., 2007. Malnutrition during lactation changes growth hormone mRNA expression in offspring at weaning and adulthood. J. Nutr. Biochem. 18, 134–139.

Muniz, P.T., Ferreira, U.M., Ferreira, C.S., Conde, W.L., Monteiro, C.A., 2002. Intestinal parasitic infections in young children in São Paulo, Brazil: prevalences, temporal trends and associations with physical growth. Ann. Trop. Med. Parasitol. 96, 503–512.

Nugent, R.A., Fathima, S.F., Feigl, A.B., 2011. The burden of chronic kidney disease on developing nations: a 21st century challenge in global health. Nephron Clin. Pract. 118, 269–277.

Nussenzveig, I., De Brito, T., Carneiro, C.R., Silva, A.M., 2002. Human Schistosoma mansoni-associated glomerulopathy in Brazil. Nephrol. Dial. Transplant. 17, 4–7.

Ots, M., Troy, J.L., Rennke, H.G., Mackenzie, H.S., Brenner, B.M., 2004. Impact of the supplementation of kidney mass on blood pressure and progression of kidney disease. Nephrol. Dial. Transplant. 19, 337–341.

Passos, M.C.F., Vicente, L.L., Lisboa, P.C., Moura, E.G., 2004. Absence of anorectic effect to acute peripheral leptin treatment in adult animals whose mothers were malnourished during lactation. Horm. Metab. Res. 36, 625–629.

Passos, M.C.F., Ramos, C.F., Moura, E.G., 2000. Short and long term effects of malnutrition in rats during lactation on the body weight of offspring. Nutr. Res. 20, 1603–1612.

Passos, M.A., Passos, M.C., Oliveira, E., Trotta, P.A., Nogueira-Neto, J.F., Bonomo, I.T., Lisboa, P.C., de Moura, E.G., 2011. Maternal prolactin inhibition during lactation is associated to renal dysfunction in their adult rat offspring. Horm. Metab. Res. 43, 636–641.

Pires, K.M., Aguila, M.B., Mandarim-de-Lacerda, C.A., 2006. Early renal structure alteration in rat offspring from dams fed low protein diet. Life Sci. 79, 2128–2134.

Ramos, E.A., Andrade, Z.A., 1987. Chronic glomerulonephritis associated with hepatosplenic Schistosomiasis mansoni. Rev. Inst. Med. Trop São Paulo 29, 162–167.

Rodrigues, V.L., Otoni, A., Voieta, I., Antunes, C.M.F., Lambertucci, J.R., 2010. Glomerulonephritis in schistosomiasis mansoni: a time to reappraise. Rev. Soc. Bras. Med. Trop. 43, 638–642.

Sadler, C.H., Rutitzky, L.I., Stadecker, M.J., Wilson, R.A., 2003. IL-10 is crucial for the transition from acute to chronic disease state during infection of mice with *Schistosoma mansoni*. Eur. J. Immunol. 33, 880–888.

Santos, W.L., Sweet, G.M., Bahiense-Oliveira, M., Rocha, P.N., 2011. Schistosomal glomerulopathy and changes in the distribution of histological patterns of glomerular diseases in Bahia, Brazil. Mem. Inst. Oswaldo Cruz 106, 901–904.

Sleigh, A.C., Hoff, R., Mott, K.E., Maguire, J.H., da França Silva, J.T., 1986. Manson's schistosomiasis in Brazil: 11-year evaluation of successful disease control with oxamniquine. Lancet 1, 635–637.

Sobh, M., Moustafa, F., Hamid, S., Ghoneim, M., 1996. Schistosomal-specific nephropathy in Syrian golden hamsters: treatment by induction of antigen excess. Nephrol. Dial. Transplant. 11, 2178–2184.

Steinmann, P., Keiser, J., Bos, R., Tanner, M., Utizinger, J., 2006. Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. Lancet Infect. Dis. 6, 411–425.

Van der Werf, M., Vlas, S.J., Broker, S., Looman, C.W.N., Nagelkerke, N.J.D., Habbema, J.D.F., Engels, D., 2003. Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa. Acta Trop. 86, 125–139.

Van Velthuysen, M.L.F., 2000. Glomerulopathy associated with parasitic infections. Clin. Microbiol. Rev. 13, 55–66.

Viana, I.R., Sher, A., Carvalho, O.S., Massara, C.L., Eloi-Santos, S.M., Pearce, E.J., Colley, D.G., Gazzinelli, G., Correa-Oliveira, R., 1994. Interferon-gamma production by peripheral blood mononuclear cells from residents of an area endemic for *Schistosoma mansoni*. Trans. R. Soc. Trop. Med. Hyg. 88, 466–470.

Vicente, L.L., Moura, E.G., Lisboa, P.C., Costa, A.M.A., Amadeu, T., Mandarim-de-Lacerda, C.A., Passos, M.C.F., 2004. Malnutrition during lactation is associated with higher expression of leptin receptor in pituitary of the adult offspring. Nutrition 20, 924–928.

Williams, M.E., Montenegro, S., Domingues, A.L., Wynn, T.A., Teixeira, K., Mahanty, S., Coutinho, A., Sher, A., 1994. Leukocytes of patients with *Schistosoma mansoni* respond with a Th2 pattern of cytokine production to mitogen or egg antigens but with a Th2 pattern to worm antigens. J. Infect. Dis. 170, 946–954.

Woods, L.L., Jr., Ingelfinger., Jr., Nyengaard., Rasch, R., 2001. Maternal protein restriction suppresses the newborn renin-angiotensin system and programs adult hypertension in rats. Pediatr. Res. 49, 460–467.

Zandi-Nejad, K., Luyckx, V.A., Brenner, B.M., 2006. Adult hypertension and kidney disease: the role of fetal programming. Hypertension 47, 502–508.

Zwingerber, K., Hohmann, A., Cardoso de Brito, M., Ritter, M., 1991. Impaired balance of interleukin-4 and interferon-gamma production in infections with *Schistosoma mansoni* and intestinal nematodes. Scand. J. Immunol. 34, 243–251.